REMARKS

I. Status of the Claims

Claims 1-35 were originally filed in the parent application. Subsequently, claims 1-10, 12, 13, and 15-35 were canceled, and claim 36 was first added and later canceled. Claims 11 and 14 remain pending.

Upon entry of the present amendment, claim 11 is amended to recite "greater than 95% sequence identity," which finds support in the specification, *e.g.*, on page 14, lines 17-18, and page 21, line 19. No new matter is introduced.

II. Claim Rejections

A. 35 U.S.C. §112, First Paragraph

Written Description Rejection

Claim 11 and 14 are again rejected under 35 U.S.C. §112, first paragraph, for alleged lack of written description. Specifically, the Examiner alleged that the specification provides inadequate description for all polypeptide monomers within the claim scope. Applicants respectfully traverse the rejection, particularly in view of the present amendment.

As amended, the pending claims are directed to a polypeptide monomer comprising an alpha subunit of a heteromeric potassium channel. The polypeptide monomer is defined by structural and functional features: the claimed polypeptide monomer (1) has the ability to form, with at least one additional Kv alpha subunit, a heteromeric potassium channel having the characteristic of voltage gating; and (2) has an amino acid sequence that has greater than 95% amino acid sequence identity to SEQ ID NO:17. As discussed in Applicants' last response filed March 26, 2007, because of the abundant knowledge relating to voltage-gated potassium channels and various methods available for amino acid sequence alignment, these structural and functional features can be readily determined by a person of skill in the art. Therefore, the description of the claimed subject matter is in full compliance with the written description requirement set forth in the prevailing case law such as *Fiers* and *Lilly*.

Furthermore, the amended claims now recite a greater than 95% sequence identity to a reference amino acid sequence, SEQ ID NO:17. As such, the claimed subject matter is more defined than that presented by the previously pending claims. In view of the general knowledge of Kv potassium channel structure and specific information obtained from sequence alignment between Kv6.2 orthologs (such as SEQ ID NO:1 and SEQ ID NO:17, filed as Exhibit A with Applicants' response of March 26, 2007), the artisan would be able to, with a reasonable level of certainty, predict or envision alternative amino acids at certain residues in functional variants derived from SEQ ID NO:17 with at least 95% sequence identity to SEQ ID NO:17. Applicants contend that a sufficiently detailed description of the claimed invention has been provided, such that "one skilled in the art can reasonably convinced that the inventor had possession of the claimed invention." MPEP §2163 I.

Taken together, Applicants contend that the specification provides a sufficiently detailed description of the claimed invention to show the inventors' possession of the invention. The withdrawal of the written description rejection is therefore respectfully requested.

Enablement Rejection (Scope-Based)

Claims 11 and 14 are also rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. Specifically, the Examiner alleged that the specification fails to provide proper enablement for all polypeptide monomers within the claim scope. Applicants respectfully traverse the rejection, particularly in view of the present amendment.

In the response filed March 26, 2007, Applicants provided detailed analysis of the fact pattern of the instant case with regard to the *Wands* factors and concluded that the claimed invention is fully enabled in light of the knowledge and techniques available in the art as well as the teaching of this application. Applicants take the position that there is no sound basis for rejecting the pending claims for lack of enablement, now that the claimed invention is more specifically defined by the amended claims.

As discussed in the response filed March 26, 2007, the prior art is in a highly advanced state with a large body of knowledge and variety of techniques, and the ordinary level

of technical skill in the relevant art is high. Such knowledge and skill confers a significant level of predictability in the relevant art. Given that the general features of a voltage-gated potassium channel subunit, both structurally and functionally, are thoroughly studied and well characterized, it is well within the purview of an artisan to modify a small number of the amino acid residues of an exemplary Kv6.2 subunit (such as one having the amino acid sequence of SEQ ID NO:17) to produce a functional variant. This is particularly true when (1) the permitted sequence variation is limited; and (2) there is sufficient information that can guide the artisan to make the modification.

The pending claims now define the claimed polypeptide monomer as having an amino acid sequence at least 95% identical to SEQ ID NO:17, in addition to its functional features. Sequence alignment between two or more Kv alpha subunit sequences (such as the one between SEQ ID NO:1 and SEQ ID NO:17, shown as Exhibit A of the response filed March 26, 2007) provides highly valuable indication to a skilled artisan which amino acid residues are likely to tolerate modification and which others are unlikely to tolerate modification, such that the artisan would not randomly mutate amino acid residues in hope of obtaining a functional variant; instead, the process of generating functional variants of SEQ ID NO:17 would be performed in a focused and guided manner, resulting in a relatively small number of variants, which have a relatively high probability of retaining the desired functionality. With the recited greater than 95% sequence identity, this probability level is now substantially higher.

As such, Applicants submit that no undue experimentation is needed for a person of skill in the art to make and use the claimed invention. Withdrawal of the enablement rejection is respectfully requested.

B. 35 U.S.C. §101 and §112

Claims 11 and 14 are also rejected under 35 U.S.C. §101 for alleged lack of patentable utility and under 35 U.S.C. §112, first paragraph, for alleged lack of enablement due to alleged lack of utility. Applicants respectfully traverse the rejections.

1. Standard to Assess Utility

According to MPEP §2107, the Examiner should review the claims and the supporting written description to determine whether the utility requirement under 35 U.S.C. §101 is met. No rejection based on lack of utility should be made if an invention has a well-established utility, *i.e.*, a utility that will be immediately appreciated by one of ordinary skill in the art based on the characteristics of the invention, regardless any such utility has been asserted. Neither should any rejection be made for lack of utility if an applicant has asserted a specific and substantial utility that would be considered credible by one of ordinary skill in the art.

In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101. MPEP §2107.02 III A. The Court of Customs and Patent Appeals stated in *In re Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

In re Langer, 183 USPQ 288, at 297 (CCPA, 1974, emphasis in original). To overcome the presumption of sufficient utility as asserted by an applicant, the Examiner must carry the initial burden to make a *prima facie* showing of lack of utility and provide a sufficient evidentiary basis for the conclusion. In other words, the Examiner "must do more than merely question operability--[he] must set forth factual reasons which would lead one skilled in the art to question objective truth of the statement of operability." *In re Gaubert*, 187 USPQ 664, 666 (CCPA 1975).

MPEP §2107.02 IV further states, a detailed explanation should be given for a utility rejection as to why the claimed invention has no specific and substantial asserted utility. Documentary evidence should be provided when possible. Otherwise the Examiner should specifically explain the scientific basis for his factual conclusions.

2. The Asserted Utility Is Specific and Substantial

The present specification provides, for the first time, the cloning of a novel potassium channel subunit, Kv6.2, which has an exemplified amino acid sequence of SEQ ID NO:17. Pending claims are drawn to a Kv6.2 polypeptide monomer, which has at least 95% sequence identity to SEQ ID NO:17 and can form a heterologous voltage-gated K^+ channel with another alpha subunit. It is specifically asserted that the K^+ channels comprising the claimed polypeptide monomers "have significant roles in maintaining the resting potential and in controlling excitability of a cell," especially in the central nervous system (CNS) such as brain (see, *e.g.*, page 8, lines 16-22, and Examples 1 and 2). The specification also states that the availability of these K^+ channel subunits would enable assay systems to identify compounds specifically modulating the activity of the channels, and that these compounds may be used in treatment of diseases relevant to altered potassium channel activities, for example, CNS disorders including migraines, hearing and vision problems, psychotic disorders, seizures. These compounds also may be useful as neuroprotective agents, for instance, to prevent stroke (see, *e.g.*, page 8, lines 23-27).

Applicants assert that the present invention has a specific utility. Specific utility is defined by the MPEP as a utility that is specific to the subject matter claimed. The MPEP explains that applications show sufficient specific utility when applicants disclose a "specific biological activity" and reasonably correlate that activity to a "disease condition." MPEP §§2107.01 and 2107.02. In the present application, Applicants disclose a "disease condition," *i.e.*, altered cell resting potential and excitability, that correlates with a "biological activity," *i.e.*, the opening and closing of the claimed voltage-gated K^+ channels. This application demonstrates that the claimed Kv6.2 channels are expressed in tissues such as the brain. The application further provides methods for identifying compounds capable of modulating Kv6.2 channel activities, which may be used for treating diseases such as migraines, seizures, or other CNS disorders. Applicants thus submit that the present invention has a specific utility, *e.g.*, the Kv6.2 channels can mediate cell resting potential and excitability in certain tissues such as the brain, which is clearly specific for the claimed Kv6.2 channels and not just any ion channels.

Applicants also assert that the present invention has a substantial utility or a "real-world" use. The present invention provides novel voltage-gated potassium channels, Kv6.2, demonstrates the Kv6.2 channel expression in certain tissues and functional features, therefore indicating the involvement of the Kv6.2 channels in modulating cellular functions in these tissues, and teaches how to identify modulators of the Kv6.2 channels. Therefore, there is a real-world use of the present invention in the modulation of cell excitability through modulation of the Kv6.2 channel activity, as well as in the identification of compounds that modulate Kv6.2 channels and thus can be useful as therapeutic agents for treating diseases related to altered cell excitability in relevant tissues, such as migraine and seizure.

3. Declaration by Dr. Krafte Establishes Utility

Although not carrying the initial burden to establish a patentable utility, Applicants nevertheless offer a Rule 132 declaration by Dr. Douglas Krafte to explain that "the identification of the coding sequence for Kv6.2, coupled with the demonstration of its functional expression, has a specific and substantial utility, which is credible to one of ordinary skill in the art, particularly for the purpose of drug discovery" (paragraph 5 of the declaration).

More specifically, Dr. Krafte attests in paragraph 6 of the declaration that several subfamilies of the Kv potassium channel family have previously been identified. These potassium channels are indicated in signal transduction during various biological processes such as neuronal integration, cardiac pacemaking, muscle contraction, hormone secretion, cell volume regulation, lymphocyte differentiation, and cell proliferation. Given this knowledge and the specific expression of Kv6.2 in the CNS, one of ordinary skill in the art would recognize the Kv6.2 channel as a therapeutic target for treating CNS disorders such as migraines, hearing and vision problems, psychotic disorders, and seizures. The identification of human Kv6.2 coding sequence makes it possible to screen for activators and inhibitors of Kv6.2 potassium channels. The ability to functionally express the channels is very important in a modern drug discovery environment and allows pharmaceutical researchers to identify compounds that directly affect the channel activity. These same compounds can then be tested in other comparable functional assays to assess selectivity and determine off-target activity and the potential for side-effects.

Because such activators or inhibitors can be used for treating conditions such as those named above, the present invention has a specific and real-world use. KCNQ2 is an example of a potassium channel as a target for therapeutic purposes. Loss of function mutations of KCNQ2 have been shown to cause a form of epilepsy (Singh *et al.*, 1998 *Nat. Genetics* **18**: 25-29, attached as **Exhibit B** of the declaration) and the KCNQ2 channels have been targets for drug discovery programs for a number of years (see, *e.g.*, Wickenden *et al.*, 2004 *Expert Opin. Ther. Patents* **14**(4): 1-13, attached as **Exhibit C** of the declaration).

Dr. Krafte goes on to explain in paragraph 7 of his declaration that it is well known in the art that once an ion channel has been identified, modulators of this ion channel can be routinely identified based on the coding sequence of the ion channel, functional expression, and a method for activation of the channel. The present application provides nucleic acid and amino acid sequences of human Kv6.2 as well as methods for detecting the activity of a Kv6.2 potassium channel, one of ordinary skill in the art can thus conduct routine testing to identify activators or inhibitors of a Kv6.2 potassium channel useful for modulating signal transduction in the cells where this potassium channel is present (*e.g.*, the brain), and therefore useful for treating CNS disorders such as migraines, hearing and vision problems, psychotic disorders, and seizures.

Insofar as the relationship between an ion channel and a specific disease is concerned, Dr. Krafte explains why a causal connection is not necessary in paragraph 8 of the declaration:

> There are known instances where modulation of an ion channel is useful for treating a specific disease even though the channel itself may not cause the disease. For example, hypertension can be caused by a variety of illnesses such as renal disease and diabetes. Among the treatment strategies for hypertension is the use of drugs such as calcium channel blockers to relax the vasculature. Relaxing the vasculature to reduce blood pressure by blocking a calcium channel is useful and effective, even if the original cause of the hypertension is unrelated to the calcium channel itself. Similarly, it is perfectly reasonable to expect that the targeting of a Kv6.2 channel,

> a voltage-gated potassium channel expressed in the brain, is an appropriate strategy for treating CNS disorders, whether or not such conditions are directly caused by altered Kv6.2 activity. Thus, the disclosure of the present application is sufficient to establish the utility of Kv6.2.

Dr. Krafte further provides reasons why he disagrees with the Examiner's contension, *i.e.*, the alleged insufficiency of the Kv6.2 sequence information for establishing utility. Dr. Krafte points out that this patent application provides not only the sequence information, but also functional expression and tissue distribution for the Kv6.2 potassium channel. Based on his experience, Dr. Kraftes finds this disclosure to provide the vital information necessary for a modern drug discovery effort where one expresses an ion channel of interest and subsequently identifies small molecule modulators of the ion channel in functional assays; the modulators can then be used for treating diseases and conditions relevant to the ion channel. Dr. Krafte attests that many of the drug discovery programs he has been associated with over the years have relied on a similar level of information and data.

In view of the declaration, Applicants contend that a specific, substantial, and credible utility has been established for the present invention.

4. The Examiner Has Not Established A *Prima Facie* Showing of Lack of Utility

The Examiner's rejection of the pending claims for alleged lack of utility is based on the statement that "the instant application does not disclose a specific biological role for the Kv6.2 protein or its significance to a particular disease, disorder, or physiological process which one would manipulate for a desired physiological of clinical effect" (see, *e.g.*, top of page 12 of the Office Action). In other words, the Examiner did not believe the specific and substantial utility asserted by Applicants.

As far as the question of utility is concerned under 35 U.S.C. §101, the MPEP places the initial burden on the Examiner, not Applicants, to provide evidence to support a factual conclusion of the credibility of an asserted utility. In fact, MPEP §2107.02 III.B. specifically cautions Office personnel that, once an assertion of a particular utility is made, "that

assertion cannot simply be dismissed ..... as 'wrong,' even when there may be reason to believe the assertion is not entirely accurate." Instead, the Examiner must provide an explanation setting forth the reasoning used in concluding that the asserted specific and substantial utility is not credible; support for factual findings relied upon in reaching the conclusion; and an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. MPEP §2107.02 IV.

On page 11 of the Office Action, the Examiner questions the asserted utility of Kv6.2 modulators for treating CNS disorders, stating that the specification does not indicate in what tissue types Kv6.2 is expressed. Citing the publication by Zhu *et al.*, the Examiner contends that the post-filing reference describes expression of Kv6.2 in myocardium, further challenges the asserted connection between Kv6.2 and CNS disorders. Applicants disagree.

First, Applicants submit that the specification does describe in what tissue type Kv6.2 is expressed. For instance, Example 2 describes the cloning of human Kv6.2 from human whole brain mRNA, clearly indicating the expression of Kv6.2 in brain tissue. Second, even though the Zhu reference (not a prior art reference) shows Kv6.2 expression in myocardium, this observation in itself does not necessarily contradict the involvement of Kv6.2 in CNS and therefore the asserted utility of the present invention. Indeed, the asserted utility is in part based on the undisputable fact that the present inventors first cloned the Kv6.2 coding sequence human whole brain mRNA.

Citing the references by Hugnot *et al.*, Castellano *et al.*, and Ottschytsch *et al.*, the Examiner further argues that, because of the great diversity of voltage-gated potassium channels in their properties and functions, and because of the existence of "functional" potassium channel subunits (those that can form homotetrameric functional channels) and "silent" subunits (those that cannot form homotetrameric function channels but can form heterotetrameric functional channels when assembled with other subunits), the precise biological function of the Kv6.2 subunit of this invention cannot be easily ascertained without further research, even though its structural features (such as the conserved K^+ selective pore region and S4-S6 domains) have

allowed its identification as a subunit belonging to the voltage-gated potassium channel family. Applicants cannot agree with the Examiner's reasoning.

First of all, although discrete genes encode for discrete polypeptide monomers, or subunits, that assemble to form functional ion channels, these native polypeptide subunits do not exist individually in a living organism without being an integral part of a functional ion channel. In other words, these individual subunits do not have a biological function independent of and separate from the ion channel they form. Indeed, as far as the "real-world" use of an invention is concerned, an ion channel subunit has the same biological function as the ion channel of which it is a part, regardless of the "functional" or "silent" nature of the subunit. Thus, for the purpose of assessing the utility of this invention, the question of functionality should be considered at the level of a fully assembled potassium channel rather than at the level of individual subunits.

Secondly, with regard to the function of a Kv6.2 potassium channel and its utility, as indicated in the specification, because of the expression of this subunit (and therefore presence of voltage-gated potassium channels comprising the subunit) in the CNS, particularly the brain, and the ability of such potassium channels in modulating cell excitability by changing cell membrane potential, an artisan would reasonably believe that these channels can serve as therapeutic targets for treatment of conditions related to aberrant cell excitability in CNS, particularly the brain. Dr. Krafte's declaration also specifically attests to this point. Since this asserted utility relies on the expression of the Kv6.2 channels in these specific tissues (*e.g.*, brain) and the potassium channels' involvement in the regulation of cellular excitability in these tissues, the present invention has a specific utility. In view of the specific conditions Kv6.2 channel modulators are believed capable of treating, and the fact that screening method for identifying these modulators are taught in the specification, an artisan can readily use the present invention without the need to carry out extensive additional research. Thus, the present invention has a substantial or "real-world" use. This is again confirmed by Dr. Krafte in his declaration from the perspective of a skilled person in the art.

The three references cited by the Examiner, on the other hand, offer discussions of how individual potassium channel subunits act either as functional subunits or regulatory (*i.e.*,

"silent") subunits in their assembly to form potassium channels. There is no discussion that specifically pertains to the Kv6.2 subunit. Furthermore, these references focus on the roles individual potassium channel subunits play in the assembly of a functional ion channel instead of the physiological roles of fully assembled potassium channels. The cited references therefore do not in any way contradict the statements in the specification and cannot adequately support a *prima facie* showing of lack of specific, substantial, and credible utility.

5. Claims Drawn to Nucleic Acids Encoding Fully Characterized Proteins Meet the Utility Requirement under 35 U.S.C. §101

The claimed Kv6.2 channels are fully characterized both structurally and functionally. The polypeptides are defined by shared structural features, *e.g.*, their amino acid sequences have at least 95% sequence identity with a reference sequence (SEQ ID NO:17), and shared functional features, *e.g.*, capable of forming a heterologous voltage-gated potassium channel with another Kv alpha subunit.

According to *the Revised Interim Utility Guidelines Training Materials* promulgated by the PTO (http://www.uspto.gov/web/menu/utility.pdf), a characterized protein has sufficient utility for patentability. This standard is made evident from Example 8 of the guidelines. In Example 8, a compound A is disclosed to inhibit enzyme XYZ, a well known enzyme, *in vitro*. The specification states that the compound A can be used to treat diseases caused or exacerbated by enzyme XYZ. No such diseases are named. Claim 1 is directed to compound A. Claim 2 is directed to a method of treating a disease caused or exacerbated by enzyme XYZ consisting of administering an effective amount of compound A to a patient. In the subsequent analysis, claim 2 is deemed to be insufficiently supported by a real world context of use. This is because neither the specification nor the art of record discloses any disease or conditions caused or exacerbated by enzyme XYZ and therefore, the asserted utility is seen as a method of treating an unspecified and undisclosed disease or condition, which does not define a "real world" context of use. Claim 1, however, is regarded as having utility because claim 1 is directed to a compound that inhibits an enzyme and enzymes have well established utility in the art, i.e., catalyzing certain reactions.

This example can be compared to the present application. The present application claims Kv6.2 potassium channel subunit polypeptides, which are analogous to compound A that inhibits enzyme XYZ. The specification indicates that Kv6.2 channels are likely involved in modulating cell excitability in certain organs such as brain. Thus, the ion channels can be used to as targets for treating disorders related to altered cell excitability in these organs. In Example 8, claim 1 directed to compound A is found to have utility even though there is no disclosure of specified disease that to be treated. Accordingly, even if the Examiner is not convinced, despite the disclosure by the present specification, that Kv6.2 channels are involved in regulation of cell excitability in the brain, a claim directed to compound A, *i.e.*, the Kv6.2 subunit polypeptides in the present case, have sufficient utility for patentability. The utility resides in the fact that the claimed voltage-gated potassium channel subunits, which, like enzymes, have a well-established utility in the art: adjusting the passage of K^+ according to varying conditions.

Analysis of pending claims according to *the Revised Interim Utility Guidelines Training Materials* therefore further supports Applicants' position that the rejection for lack of utility is improper.

6. The Utility Rejection Creates an Inconsistency in PTO Policy

Moreover, Applicants contend that the utility rejection is improper because such rejection would create a significant inconsistency in the USPTO policy regarding the utility requirement. This application is a division of USSN 09/719,919, which matured into U.S. Patent No. 6,680,180 and is therefore presumed to meet the utility requirement under 35 U.S.C. §101. The claims of this application are drawn to polypeptides, whereas the claims of the '180 patent are drawn to nucleic acids. To maintain the utility rejection in this case would lead to an irreconcilable contradiction in the PTO practice.

In summary, Applicants do not believe that the utility rejection and the utility-based enablement rejection are proper and therefore respectfully request their withdrawal.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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